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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/263,689	03/05/99	NI J	1488.0560002

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EXAMINER	
CANELLA,K	
ART UNIT	PAPER NUMBER
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/263,689	NI et al
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *24-27, 68-70, 77-80, and 90-140* is/are pending in the applicat

Of the above, claim(s) *24-27, 68-70, and 77-80* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *90-140* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachm nt(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Acknowledgment is made of applicant's election with traverse of Group I, claims 62-67 and 90-127, drawn to the polypeptides comprising SEQ ID NO:4, and pharmaceutical compositions thereof. The traversal is on the grounds that the restriction is improper, that the searches of Groups I through VIII would substantially overlap and not constitute a serious search burden. This is not found persuasive. The inventions of Groups I, II, V and VI are structurally and functionally distinct. Further, these molecules are classified differently than the invention of Group I necessitating different searches in the U.S. Patent Shoes and requiring the consideration of different patentability issues. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. Further, the methods of Groups III, IV, VII and VIII differ in method objectives, method steps and parameters and reagents used.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 62-67 have been canceled. Claims 128-140 have been added. Claims 24-27, 68-70, 77-80 and 90-140 are pending. Claims 24-27, 68-70 and 77-80, drawn to non-elected inventions, are withdrawn from consideration. Claims 90-140 are examined on the merits.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 90-140 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility. The specification does not teach that the polynucleotide sequence of SEQ ID NO:3 is actually translated into protein which is expressed in any disease state. The specification teaches that the polynucleotides of SEQ ID NO:3 was isolated from a cDNA library derived from pancreatic tumor, and that SEQ ID NO:1, 3, 5 and 7 were detected in cDNA libraries from pancreas, colon, small intestine, brain, bone marrow, kidney, lung, spleen and testes tissue (pg. 7, lines 9-16). It is assumed, since it is not stated otherwise, that the pancreas, colon, small intestine, brain, bone marrow, kidney, lung, spleen and testes tissue cDNA libraries were made up of both tumor and non-tumor tissue. Thus, this does not constitute evidence of tumor-specific expression of the disclosed polynucleotides. Although the specification suggests on pg 49, beginning with line 7, that the polynucleotides designated as galectins 8, 9, 10 or 10 SV can be used in Northern blot analysis with MTM blots to examine tissue distribution of the disclosed polynucleotides, the specification does not relay any data resulting from the use of the disclosed polynucleotides with actual clinical samples. Further, the specification is completely devoid of evidence linking the expression of the polypeptide of SEQ ID NO:4, or lack thereof, with a pathological state. Even if the expression of the polynucleotide of SEQ ID NO:3 did correlate with a disease state, one of skill in the art would, recognize that expression of mRNA does not dictate the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other

proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if SEQ ID NO:3 were in fact translated into the polypeptide of SEQ ID NO:4.

Asserted utilities for the hypothetical galectin 9 polypeptides include therapy and diagnosis of conditions and diseases characterized by aberrant growth regulatory activity such as autoimmune diseases, cancer, inflammatory disease, wound healing, arteriosclerosis and other heart diseases, microbial infection, asthma and allergic diseases. These asserted utilities of the disclosed galectins 8, 9, 10 and 10SV are based on the observation that the putative galectin 8, 9, 10 and 10SV share sequence homology with other galectins (figure 5) and in particular, galectin 1 is known to induce apoptosis of T-cells and T cell leukemias, and galectin 3 is known to confer resistance to apoptosis in cultured cells. However, even if the polynucleotide of SEQ ID NO:3 were translated into galectin 9 as SEQ ID NO:4, there is no evidence in the specification, or any art of record to indicate that galectin 9 would be capable of regulating apoptosis in a positive or negative manner, or that the expression of galectin 9, or lack thereof, would be diagnostic for any disease state. Clearly the galectins of 1 and 3, although having the common property of beta-

galactoside-binding, exhibit widely differing functions as evidenced by galectin 1 promoting apoptosis and galectin 3 resisting apoptosis. Even if recombinantly produced SEQ ID NO:4 would have the property of binding beta-galactosides, this does not dictate that SEQ ID NO:4 would function in any apoptotic pathway. Further, even if the disclosed hypothetical proteins share sequence homology with other galectins, they also exhibit sequence dissimilarities and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, Vol. 257, pp.1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Biology, 1990, Vol. 11, pp. 2129-2138) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

Clearly, the function or tissue distribution of the hypothetical SEQ ID NO:4 polypeptide could not be predicted, based on sequence similarity with galectins 1-7, nor would it be expected to be the same as that of any of the galectins 1-7. In addition, Bork (Genome Research, 2000, Vol.10, pp.398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational

modification and cellular context on protein function as taught by Bork, the function or tissue distribution of the putative SEQ ID NO:4 polypeptide could not be anticipated.

The specification discusses the administration of hypothetical galectins 8, 9, 10 and 10SV for therapy of conditions and diseases characterized by aberrant growth regulatory activity such as autoimmune diseases, cancer, inflammatory disease, wound healing, arteriosclerosis and other heart diseases, microbial infection, asthma and allergic diseases. However, the specification is completely devoid of objective evidence regarding the successful treatment or modulation of any disease in any subject by the administration of the claimed polypeptides. Other asserted utilities for the hypothetical polypeptide of SEQ ID NO:4, such as the production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide sequences and therefore are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:4. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptides.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 13 and 25 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

7. In the event that Applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to the polypeptides comprising SEQ ID NO:4, pharmaceutical compositions and recombinant production thereof, because the specification does not reasonably provide enablement for a polypeptides comprising fragments of

SEQ ID NO:4, proteins comprising amino acid sequences which are at least 95% identical to SEQ ID NO:4 or proteins comprising amino acids which are encoded by polynucleotides that hybridize to SEQ ID NO:3 or the complement thereof. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A)As drawn to proteins comprising amino acid sequences which are at least 95% identical to SEQ ID NO:4

Claims 90, 92, 94-98, 100, 102-105, 128 and 129 are drawn to proteins comprising polypeptide variants of SEQ ID NO:4. Clearly, for the reasons set forth in paragraphs 5 and 6 supra, the specification is not enabled for claims drawn to polypeptides comprising SEQ ID NO:4, therefore the specification has not enabled the scope of the claims drawn to polypeptide variants of SEQ ID NO:4. Further, these claims encompass polypeptide sequences which differ from the disclosed polypeptide sequence, and the specification gives no guidance on or exemplification of how to make/use the broadly claimed polypeptides. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al. (Journal of Cell Biology, 1990, Vol. 111, pp. 2129-2138), replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. (Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that a polypeptide that differs from SEQ ID NO:4 by as much as 5% would function as suggested. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be

predicted from the disclosure how to make/use variant polypeptides of SEQ ID NO:1-5. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

(B)As drawn to proteins comprising fragments of SEQ ID NO:4

Claims 106-127 and 130-132 are drawn to proteins which comprise fragment of the putative SEQ ID NO:4 and proteins which comprise a fragment of SEQ ID NO:4, said protein exhibiting a lactose binding property. Clearly, for the reasons set forth in paragraphs 5 and 6 supra, the specification is not enabled for claims drawn to polypeptides comprising SEQ ID NO:4, therefore the specification has not enabled the scope of the claims drawn to proteins comprising fragments of SEQ ID NO:4. Further, the specification does not demonstrate that insertion of fragments of the putative SEQ ID NO:4 into a different amino acid context would result in a polypeptide with any of the asserted attributes of the hypothetical galectin 9 such as the modulation of apoptosis.. It is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the SEQ ID NO:4 polypeptide can potentially profoundly alter the three dimensional structural environment in which the given fragment is located (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem") thus, the consequences of the altered sequence environment on the fragment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects, such as membrane anchorage, protein activation and sub-cellular location must be considered with respect to protein function in addition to molecular aspects (Bork, p. 398, col 2). Due to these reasons, one of skill

in the art would be forced into undue experimentation in order to practice the invention as claimed.

(C)As drawn to proteins encoded by polynucleotides which hybridize to the protein coding region of SEQ ID NO:3 or the complement thereof.

Claims 133-140 encompass proteins comprising amino acid sequences encoded by polynucleotides comprising non-disclosed nucleic acid sequences attached to polynucleotides that encode SEQ ID NO:4, that is polynucleotides that hybridize to SEQ ID NO:3 and the complement thereof, under specific hybridization conditions. As disclosed above, the specification does not teach how to use SEQ ID NO:4. Clearly, since the specification has not taught how to use said polypeptide, the specification has not enabled the scope of the instant claims which are drawn to proteins comprising amino acids which are encoded by polynucleotides that hybridize to SEQ ID NO:3 or the complement thereof. Listing the hybridization conditions is not limiting. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of polypeptide variants and it would be expected that a substantial number of the hybridizing or complementary polynucleotides encompassed by the claims would not encode protein which would share either the structural or asserted functional properties with the hypothetical SEQ ID NO:4, (see explanation given in paragraph A supra). Further, only one strand of SEQ ID NO:3 would encode the polypeptide of SEQ ID NO:4. If SEQ ID NO:3 is indeed the sense strand, then polynucleotides which hybridize to SEQ ID NO:3 would yield anti-sense strands, encoding polypeptide that would not remotely resemble SEQ ID NO:4 The specification fails to provide an enabling disclosure for how one would use such proteins. The specification provides insufficient guidance with regard to these issues and provides no working examples which would give guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 114 and 119 are rejected under 35 U.S.C. 102(b) as being anticipated by Massa et al (Journal of Biological Chemistry, 1995, Vol. 270, pp. 5032-5038) as evidenced by Accession Number P47967. Claims 114 and 119 are drawn to an isolated protein comprising 15 contiguous amino acids of SEQ ID NO:4 , which comprises a heterologous polypeptide. Massa et al disclose a protein comprising 20 contiguous residues of SEQ ID NO:4 which further comprises rat galectin-5.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GEETHA P. BANSAL
PRIMARY EXAMINER

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

January 28, 2001